GLAXOSMITHKLINE v TAKEDA

Actos mailing

GlaxoSmithKline complained about a mailing issued by Takeda which notified GPs that Actos (pioglitazone) could now be used in combination with insulin in type 2 diabetics with insufficient glycaemic control on insulin for whom metformin was inappropriate. The mailing also referred to Competact, a fixed-dose combination of pioglitazone and metformin. GlaxoSmithKline noted that Competact was contraindicated for use in combination with insulin.

GlaxoSmithKline complained about a number of matters and referred to inter-company dialogue. It disclosed, however, that agreement had been reached on some of the matters and so these did not proceed. With regard to another three matters, Takeda acknowledged that it had had inter-company dialogue on all of them but stated that it had reached agreement on two. Nonetheless, Takeda's response to the Authority covered all three points and the Panel ruled on all three. Takeda appealed the Panel's rulings on two of the points on the basis that the companies had previously come to an agreement on them and thus they should not have been considered by the Panel.

Paragraph 5.2 of the Constitution and Procedure stated that 'A complaint from a pharmaceutical company will be accepted only if the Director is satisfied that the company concerned has previously informed the company alleged to have breached the Code that it proposed to make a formal complaint and offered inter-company dialogue at a senior level in an attempt to resolve the matter but that this offer was refused or dialogue proved unsuccessful. A formal statement detailing the actions taken must be provided'.

In relation to GlaxoSmithKline's complaint about three separate matters the Panel ruled breaches of the Code. On appeal the Appeal Board was concerned that in inter-company correspondence Takeda had responded slowly and GlaxoSmithKline had not been justified in seeking a 'written undertaking' on matters agreed by Takeda, nonetheless given that a complaint could only proceed if inter-company dialogue had not been successful, the Panel's rulings on the two points where agreement had been reached, were declared a nullity; they would no longer stand.

The only matter upon which the companies had not agreed related to Competact. GlaxoSmithKline considered that as the mailing at issue was intended to highlight the new indication for Actos ie concomitant use with insulin, then any mention of Competact should be qualified with a statement that it was contraindicated for use in combination with insulin.

GlaxoSmithKline had serious concerns about the unqualified mention of Competact in this promotional context, and alleged that this misrepresented the situation and was not in accordance with the terms of Competact's marketing authorization.

The Panel noted that the Competact summary of product characteristics (SPC) stated that it was contraindicated for use in combination with insulin. The Panel noted that a treatment algorithm in the Actos mailer outlined five distinct treatment options for type 2 diabetics, in five vertical columns. The final purple box in four of the five vertical columns read either 'Rx Actos' or 'Add Actos'. The final box in the third column was pink, rather than purple and read 'Rx Competact'. This was followed by 'Competact: Actos + metformin combination tablet'. The Panel considered that within the context of a mailing which addressed the treatment of type 2 diabetics and highlighted the fact that Actos had now been licensed to be used in combination with insulin in type 2 patients with insufficient glycaemic control on insulin, the failure to state the relevant contraindication was misleading and inconsistent with the Competact SPC. The Panel noted Takeda's submission that the reason the contraindication had not yet been removed to bring it in line with Actos was an administrative matter, however promotion had to be in accordance with the marketing authorization and not inconsistent with the SPC. Breaches of the Code were ruled.

Upon appeal by Takeda the Appeal Board noted that an arrow ran along the bottom of the algorithm from left to right marked 'Progression of Type 2 diabetes'. The first time that insulin was introduced as a treatment option was in the last box on the right hand side. The last vertical column stated in successive boxes '… on insulin', 'metformin contraindicated or not tolerated', 'WHAT NEXT?', 'Add Actos', and finally below the last box 'Actos + insulin combination therapy'.

The Appeal Board considered that the inclusion of Competact in the treatment algorithm without noting its contraindication for use in combination with insulin was not misleading, as its treatment position of type 2 diabetics in the algorithm at position three was before the introduction of insulin at position five.

The Appeal Board further noted that that Competact was a combination of pioglitazone and metformin neither of which were contraindicated with insulin. Thus the absence of the contraindication in this instance should not give rise to safety issues. The Appeal Board ruled no breaches of the Code. The appeal was successful.

GlaxoSmithKline UK Limited complained about a four page mailing (ref AC070230) for Actos (pioglitazone) issued by Takeda UK Limited which notified GPs of the addition of a new indication. GlaxoSmithKline supplied Avandia (rosiglitazone).

GlaxoSmithKline explained that the Actos marketing authorization had recently been extended with the addition of the following: 'Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance'. (Section 4.1 of the Actos summary of product characteristics (SPC)).

The mailing also referred to Competact, a fixed-dose combination of pioglitazone and metformin, which was also marketed by Takeda. In the context of the mailing at issue GlaxoSmithKline noted that the Competact SPC Section 4.2 Contraindications stated: 'Competact is also contraindicated for use in combination with insulin'.

Takeda explained that prescribing Actos in combination with insulin was likely to be initiated in secondary care rather than in primary care and hence this mailer was intended to alert GPs that they might see patients coming to them from secondary care on this combination.

GlaxoSmithKline complained about a number of matters and referred to inter-company dialogue. It disclosed, however, that agreement had been reached on some of the matters and so these did not proceed. With regard to another three matters, Takeda acknowledged that it had had inter-company dialogue on all of them but stated that it had reached agreement on two. Nonetheless, Takeda's response to the Authority covered all three points and the Panel ruled on all three. Takeda appealed the Panel's rulings on two of the points on the basis that the companies had previously come to an agreement on them and thus they should not have been considered by the Panel.

Paragraph 5.2 of the Constitution and Procedure stated that 'A complaint from a pharmaceutical company will be accepted only if the Director is satisfied that the company concerned has previously informed the company alleged to have breached the Code that it proposed to make a formal complaint and offered inter-company dialogue at a senior level in an attempt to resolve the matter but that this offer was refused or dialogue proved unsuccessful. A formal statement detailing the actions taken must be provided'.

In relation to GlaxoSmithKline's complaint about three separate matters on which the Panel ruled breaches of the Code, the Appeal Board noted that the full documentation on inter-company dialogue had not been submitted until the appeal and considered that without this new material it would have been difficult to decide what had been agreed. The Appeal Board considered that it would be helpful if the Director had been clearer in documenting the decision regarding which matters were to proceed as complaints. The Appeal Board was not reviewing the Director's decision. It was reviewing whether the Panel was correct to rule on the complaint.

The Appeal Board noted that Takeda had confirmed by email on 20 April that it agreed to: 'reflect the licence wording on all future pieces concerning the licence in combination with insulin as per the minutes' and '… to review the wording used in relation to adverse events and safety in relation to the use of Actos in combination with insulin as noted in the minutes. We will ensure that the wording used adequately reflects the new SmPC …' (points 1 and 3). Thus the only outstanding issue was Takeda's decision not to include the contraindication of Competact with insulin in the treatment algorithm on page 2 of the mailing. The Appeal Board noted that on 24 April GlaxoSmithKline had asked Takeda to confirm its confirmed actions points 1 and 3 (noted above) by written undertaking. In addition the email noted that GlaxoSmithKline would proceed to the PMCPA on point 2 as no agreement had been reached. Takeda had confirmed its email of 20 April on 2 May by email; this was the same day that GlaxoSmithKline complained to the PMCPA.

The Appeal Board was concerned about the behaviour of each company as evidenced in the inter-company dialogue. Takeda had been rather slow to respond to emails from GlaxoSmithKline. Nonetheless the Appeal Board considered that Takeda's emails of 20 April and 2 May had provided sufficient confirmation that agreement had been reached on points 1 and 3. GlaxoSmithKline had not been justified in seeking a 'written undertaking' on matters clearly agreed by Takeda. The Appeal Board noted that the Director had been correct to rule that the complaint should proceed only in relation to those points responded to by Takeda on which no agreement was reached. This meant that the complaint should have proceeded on one point only and not the other two. The Appeal Board thus declared the Panel's rulings on two of the points a nullity; they would no longer stand and are therefore not included in this report.

The Appeal Board considered that GlaxoSmithKline's decision to complain about matters upon which agreement had been reached was regretable. In the Appeal Board's view, any complaint submitted to the Authority should be absolutely clear about the status of inter-company dialogue.

COMPLAINT

GlaxoSmithKline noted that the second page of the mailing featured an algorithm for the treatment of type 2 diabetes. This included a highlighted mention of Competact, Takeda's pioglitazone/metformin combination. Competact was contraindicated with insulin. As the mailing was self-evidently intended to principally draw attention to the new pioglitazone indication for concomitant use with insulin GlaxoSmithKline's strong view was that any mention of Competact should be qualified with a comment drawing the prescriber's attention to the fact that

Competact was contraindicated for use in combination with insulin.

GlaxoSmithKline had serious concerns about the unqualified mention of Competact in this promotional context, and alleged that this misrepresented the situation and was not in accordance with the terms of Competact's marketing authorization in breach of Clauses 3.2 and 7.2 of the Code.

RESPONSE

Takeda explained that the second page of the mailing set the new indication into context with the other licensed indications for pioglitazone as there had been two recent changes to the licence (combination with insulin and triple combination therapy). As a result there were five separate indications/treatment pathways which could confuse prescribers, particularly those in primary care for whom Takeda did not have a permanent field force. (Takeda employed a very small group of regional account directors who saw a very small percentage of all GPs in addition to health professionals in primary care trusts and secondary care.)

It was clear in the algorithm that each vertical column represented a separate prescribing scenario. Hence in accordance with the licence the algorithm was set up at the top with the express caveat of 'In patients requiring additional glycaemic control ...' and this read on to each column separately. The far right column represented the new indication and it was clear from the words used and the display of the prescribing situations that this was the only part of this algorithm which related to the new licence.

In addition, Takeda also marketed Competact (pioglitazone/metformin) for use in type 2 diabetics and this was included in the algorithm to demonstrate to doctors where it fitted in the whole spectrum of treatment options available. Apart from this one mention in the algorithm, there were no claims about Competact in the mailing and the one column containing the prescribing scenario for Competact was clearly distinct from the Actos columns.

The algorithm clearly detailed the various licence options involving pioglitazone in an easy to read form so that the prescriber could readily determine the exact positioning of pioglitazone in all possible treatment settings. There was no mention of insulin in the section relating to the use of Competact. The Competact section read: 'In patients requiring additional glycaemic control ... on maximum tolerated dose of metformin …. Preference for minimum tablets …. What next? ... prescribe Competact'. In addition the contraindication with insulin was stated in the Competact prescribing information on page 4. In addition neither of the components of Competact (Actos and metformin) was contraindicated for use in combination with insulin. As such there was no implication for patient safety.

The fact that the contraindication for Competact had not yet been removed to bring it in line with Actos was an administrative matter, in that the submission for this change could only be made after the licence change was approved for Actos. Apart from this one mention in the algorithm, there were no claims made concerning Competact in the mailing and hence Takeda did not consider it necessary to make any additional qualification as the prescribing information for Competact was on the back page of the mailing.

PANEL RULING

The Panel noted that Section 4.3 of the Competact SPC stated that it was contraindicated for use in combination with insulin. The Panel noted that the Actos treatment algorithm outlined five distinct treatment options for type 2 diabetics, in five vertical columns. The final purple box in four of the five vertical columns read either 'Rx Actos' or 'Add Actos'. The final box in the third column was pink, rather than purple and read 'Rx Competact'. This was followed by 'Competact: Actos + metformin combination tablet'. The Panel considered that within the context of a mailing which addressed the treatment of type 2 diabetics and was designed to highlight a change in the licence whereby Actos had now been licensed to be used in combination with insulin in type 2 patients with insufficient glycaemic control on insulin, the failure to state the relevant contraindication was misleading and inconsistent with the Competact SPC. The Panel noted Takeda's submission that the reason the contraindication had not yet been removed to bring it in line with Actos was an administrative matter, however promotion had to be in accordance with the marketing authorization and not inconsistent with the SPC. Breaches of Clauses 3.2 and 7.2 were ruled.

APPEAL BY TAKEDA

Takeda submitted that the aim of the mailing was to tell primary care health professionals that, due to a recent licence extension, Actos could now be used in combination with insulin. This specific aim was made very clear, and was consistently referred to throughout the document.

Takeda submitted that UK clinical practice was such, that apart from GPs with a special interest, primary care health professionals were not routinely involved in the active management of insulin treatment in patients with type 2 diabetes. Therefore it was important that widespread notification, in the form of the mailer, was sent to all the generalist primary care physicians in the UK so as to avoid any confusion in the use of Actos with insulin, which until recently had been contraindicated. Takeda submitted that the change from a specific contraindication to an indication was really quite rare in regulatory terms and could potentially cause major confusion in primary care; patients could be taken off therapies which had been initiated in secondary care to the detriment of their glycaemic control.

Promotional information was, however, sent to secondary care health professionals including GPs with a special interest in diabetes, by means of a

mailer which focussed solely on the new indication for Actos and which included the clinical data on which this licence change was based.

Takeda submitted that given the recent, numerous licence changes for Actos, the mailer was designed to place in context all of the available treatment options for pioglitazone, so as to give the physician a more simplified overview to help them make the appropriate prescribing choices. As Competact was a relatively new available fixed-dose combination of pioglitazone/metformin, the treatment algorithm as shown on page 2 would be incomplete if some reference to it were not included. This was the only time that Competact was mentioned in the mailer, which clearly was not designed to specifically promote it and for which other mailers had been used to undertake this role. At no point did the mailer allude to any change in the licence for Competact.

Takeda submitted that in terms of its purpose being one of notification the mailer was quite clear as to its intent as follows: 'Actos. The ONLY glitazone with a licensed indication for use in combination with insulin'; 'What does this licence change mean for you and your patients?' and 'Actos; Helping insulin to reduce HbA_{1C}'.

Takeda submitted that the claims were all related to Actos, with no mention of Competact, and the licence change was referred to in the singular rather than the plural. Finally, the Actos logo was at the bottom of the page and the mailer was in the Actos brand colours, not the Competact ones.

Takeda submitted that the third page of the mailer clearly set out the context for the new licensed indication for Actos, as it stated 'This newly licensed indication provides diabetes specialists with a strong rationale to prescribe Actos in combination with insulin when metformin is contraindicated or not tolerated', 'Consequently you may see patients who are treated in secondary care receiving Actos + insulin therapy'. Once again the reference to the licence change was purely related to Actos, not to Competact, and the page was in the Actos brand colours with the Actos brand logo.

Takeda submitted that the treatment algorithm had been included to clarify the therapeutic indications as written in Section 4.1 of the Actos and, for the reason stated above, Competact SPCs. It was for this reason alone that Competact prescribing information had been included. Indeed if this was even considered to be an abbreviated advertisement for Competact, then in accordance with Clause 5 of the Code, the contraindications for use would not need to be specifically stated. In clinical practice it was acknowledged that treatment algorithms gave the indication for use of a particular product or therapy rather than their contraindications for use, and this format was followed on page 2.

Takeda submitted that the new licensed indication for Actos was, in any case, very different to the sole and unchanged licensed indication for Competact. This was clearly indicated in the treatment algorithm; for the new licensed indication it was stated that: 'Actos can only be given to Type 2 diabetes patients who are already on insulin, and for whom metformin is contraindicated or not tolerated'. This was quite different to the licence for Competact which stated 'Competact can only be given as a form of dual oral therapy to patients who are on the maximum tolerated dose of metformin'.

Takeda submitted that thus there was no scope for confusion between the two licensed indications as patients on insulin, requiring further glycaemic control, could only be given Actos (not Competact) for, as the treatment algorithm clearly showed metformin (one of the components of Competact) must be contraindicated or not tolerated in this situation. Similarly for the Competact arm of the algorithm there was no mention of a progression in treatment to include insulin.

COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline disagreed that, apart from GPs with a special interest in diabetes, primary care health professionals were not routinely involved in the active management of insulin treatment in type 2 diabetics. Diabetes formed part of the Government's Quality and Outcome Framework targets and so many GPs would be involved in the active management of these patients to ensure target HbA_{1C} levels were met. GlaxoSmithKline noted that one university ran a course specifically to train such health professionals. Non-specialist GPs would review patients on insulin and consider whether to add pioglitazone to those with insufficient glycaemic control (when metformin was inappropriate because of contraindications or intolerance).

Takeda stated that the change from a specific contraindication to an indication had the potential to cause confusion in primary care. Following on from this argument, GlaxoSmithKline strongly believed that the promotion of a new indication for Actos for which Competact was contraindicated in an item where both products were mentioned, had the ability to confuse and mislead if the contraindication with insulin for Competact was not mentioned. Health professionals might believe that Competact also had a licence with insulin, leading to prescribing that might jeopardise patient safety.

GlaxoSmithKline noted that the piece was clearly entitled as an Actos promotional leaflet in combination with insulin. GlaxoSmithKline alleged that by including Competact within the leaflet without clarity regarding the specific contraindication was misleading. As such GlaxoSmithKline agreed with the Panel's ruling in this regard and found Takeda's insistence that this was an Actos piece further reinforcement regarding the inappropriate inclusion of Competact.

GlaxoSmithKline alleged that the algorithm had a clear arrow indicating progression of type 2 diabetes, which one would then assume for treatment

progression with addition of multiple agents. It would be common clinical practice for prescribers to change patients from Actos to Competact then add in additional therapies when required, such as insulin, however there was no clarification or indication to a prescriber that this combination was contraindicated. GlaxoSmithKline additionally disagreed that the flow chart on page 2 was a genuine treatment algorithm. A treatment algorithm would refer to a wide range of products and be referenced to guidelines. As a free standing piece this could not be considered to be an abbreviated advertisement. As such GlaxoSmithKline alleged that Takeda's arguments in this regard were not relevant as each piece had to stand on its own merits and not those of a hypothetical piece of abbreviated advertising.

APPEAL BOARD RULING

The Appeal Board noted that the Actos treatment algorithm outlined five distinct treatment options for type 2 diabetics, in five vertical columns. The final box in the third column was pink, rather than purple and read 'Rx Competact'. This was followed by 'Competact: Actos + metformin combination tablet'. The Appeal Board noted that an arrow ran along the bottom of the algorithm from left to right marked 'Progression of Type 2 diabetes'. The first time that insulin was introduced as a treatment option was in the last box on the right hand side. The last vertical column stated in successive boxes '… on insulin', 'metformin contraindicated or not tolerated', 'WHAT NEXT?', 'Add Actos', and finally below the last box 'Actos + insulin combination therapy'.

The Appeal Board considered that the inclusion of Competact in the treatment algorithm without noting its contraindication for use in combination with insulin was not misleading, as its treatment position of type 2 diabetics in the algorithm at position three was before the introduction of insulin at position five.

The Appeal Board further noted that that Competact was a combination of pioglitazone and metformin neither of which were contraindicated with insulin. Thus the absence of the contraindication in this instance should not give rise to safety issues.

The Appeal Board noted that although the mailing addressed the treatment of type 2 diabetics and was designed to highlight a change whereby Actos was now licensed to be used in combination with insulin in type 2 patients with insufficient glycaemic control on insulin for whom metformin was contraindicated or not tolerated, the failure to state the relevant contraindication for Competact was not misleading. The Appeal Board ruled no breach of Clauses 3.2 and 7.2. The appeal on this point was successful.

Complaint received	**8 May 2007**
Case completed	**4 October 2007**